UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

INVITAE CORPORATION, *Plaintiff*, v. NATERA, INC., *Defendant*.	)	Case No. _____ **JURY TRIAL DEMANDED**

COMPLAINT FOR PATENT INFRINGEMENT

Plaintiff Invitae Corporation ("Invitae" or "Plaintiff") for its complaint against Defendant Natera, Inc. ("Natera" or "Defendant") alleges as follows:

NATURE OF THE ACTION

1. This action arises under 28 U.S.C. §§ 1331 and the United States Patent Act, 35. U.S.C. § 100 *et seq.*

2. Plaintiff brings this action to halt Natera's infringement of U.S. Patent No. 10,604,799 ("the '799 Patent") (attached hereto as Exhibit 1) pursuant to its rights under the Patent Laws of the Unites States, 35 U.S.C. § 1, *et seq.*

THE PARTIES

3. Invitae is a corporation organized and existing under the laws of the State of Delaware, and is the owner of the '799 Patent pursuant to a March 2021 assignment agreement appearing at Reel/Frame No. 055921/0838 of the USPTO Patent Assignment Database.

4. Invitae is a leading medical genetics company whose mission is to bring comprehensive genetic information into mainstream medicine to improve healthcare for billions

of people. Invitae's goal is to aggregate the world's genetic tests into a single service with higher quality, faster turnaround time, and lower prices.

5. On information and belief, Natera is a company organized and existing under the laws of Delaware, with its principal place of business at 201 Industrial Rd., San Carlos, California 94070. Natera provides a non-invasive test for minimal residual disease that it markets under the tradename "Signatera™." On information and belief, Natera performs the Signatera™ test at its facility in San Carlos, California.

JUSRISDICTION AND VENUE

6. This action arises under the Patent Laws of the United States of America, 35 U.S.C. § 1 *et seq.* This Court has federal question jurisdiction under 28 U.S.C. § 1331 and 28 U.S.C. § 1338(a) because this is a civil action arising under the Patent Act.

7. This Court has personal jurisdiction over Natera because Natera is incorporated in Delaware. Natera has purposefully availed itself of the benefits and protections of Delaware state law by incorporating under Delaware law.

8. This Court also has jurisdiction over Natera because Natera has availed itself of this forum, initiating civil actions in this jurisdiction, including *Natera, Inc. v. ArcherDX, Inc., et al.*, C.A. 20-125 LPS (D. Del. 2020).

9. Venue is proper in this District under 28 U.S.C. §§ 1391(b) and (c), and 1400(b) because Natera is a Delaware corporation, and Delaware is a convenient forum for resolution of the parties' disputes set forth herein.

BACKGROUND

10. Plaintiff repeats and re-alleges the foregoing paragraphs as if set forth specifically herein.

11. The '799 Patent is entitled "Sequence Assembly," and the claimed inventions were invented by Gregory Porreca and Caleb Kennedy, leading researchers in DNA sequencing technology and genomics. The '799 Patent claims and discloses novel techniques for improving the performance of DNA sequencing technology by allowing researchers to better extract the full scope of available information that results from modern DNA sequencing platforms so that mutations in an individual's DNA can be identified with enhanced specificity.

12. As the '799 Patent explains, "[n]ext-generation sequencing (NGS) technologies include instruments capable of sequencing more than 10^{14} kilobase-pair (kbp) of DNA per instrument run. Sequencing typically produces a large number of independent reads, each representing anywhere between 10 to 1000 bases of the nucleic acid." Ex. 1 at 1:28-33. To determine whether the DNA carries a mutation, however, these "independent reads" must be reassembled into stretches of DNA sequence of sufficient length to reveal the presence of the mutation.

13. As the '799 Patent explains, prior art techniques for utilizing such DNA sequence information were "problematic," and suffered from accuracy problems such that it was impossible to detect certain kinds of key mutations using DNA sequencing technology:

> Another sequence assembly technique involves aligning each individual read to a reference. This assembly technique is problematic because very short reads (e.g., 50 bp or less) may align well in a number of places on a very long reference (e.g., 5 million bp). With a number of equally good positions to align to, aligning a read to a reference offers little positional accuracy. Also, particularly with very short reads, long indels can be difficult or impossible to detect.

Id. at 2:7-14.

14. Likewise, the '799 Patent explains that existing techniques for reassembling the independent sequence reads did a "poor job" of interpreting certain kinds of mutations:

> Existing methods of read assembly do not offer the positional accuracy of a contig-based alignment while including detailed information from each read. Further, due

> to limitations in alignment algorithms, existing methods do a poor job of correctly interpreting certain mutations (e.g., indels near the ends of reads, substitutions near indels).

Id. at 2:21-26. More specifically, the '799 Patent explains that existing techniques imposed an undesirable trade-off between detecting different kinds of mutations:

> Existing approaches to alignment involve algorithms with good mismatch sensitivity at the expense of indel sensitivity or good indel sensitivity at the expense of mismatch sensitivity. For example, if an alignment is to detect mismatches with sufficient fidelity, then it is likely that some indels will be missed.

Id. at 1:62-67.

15. In view of these problems, the '799 Patent teaches and claims a new technique for improving DNA sequencing technology by enhancing sequence read assembly. Representative claim 1 of the '799 Patent is listed below:

> 1. A method for assembling sequence reads, the method comprising:
>
> obtaining a sample comprising template nucleic acid;
>
> sequencing the template nucleic acid to generate a plurality of sequence reads;
>
> inputting a reference genome and said plurality of sequence reads into
>
> a computer system comprising a processor coupled to a non-transitory memory to perform the steps of:
>
> assembling a contig from at least some of the plurality of sequence reads;
>
> identifying a plurality of contig:reference descriptions of mutations by aligning the contig to said reference genome;
>
> identifying a plurality of read:contig descriptions by aligning each of the plurality of sequence reads to the contig; and
>
> combining the contig:reference descriptions with the read:contig descriptions to produce read:reference descriptions to map positional information of mutations found in the individual reads relative to the reference.

Briefly, the claimed techniques of the '799 Patent utilize a multi-step assembly approach in which DNA sequencing reads are grouped into "contigs" and aligned to a reference genome, and then the original individual reads are re-aligned to the "contigs." The resulting alignments are then utilized to generate precise positional information regarding the locations of mutations in the

sample DNA. Far from being routine or conventional, this approach reflected a novel advance that has become widely adopted in the industry to improve the performance of DNA sequencing technology.

16. The claimed techniques of the ’799 Patent are not directed to an abstract idea or natural law, but are rather directed to a concrete technique that is used solely in conjunction with DNA sequencing technology of the kind that generates multiple independent reads. The claimed invention improves upon and realizes the full potential of such DNA sequencing technology. In this regard, the claimed techniques of the ’799 Patent expressly require “obtaining a sample comprising template nucleic acid,” and then “sequencing” the “template nucleic acid” to generate a “plurality of sequence reads.” In particular, the claimed inventions improve upon the predominant technology platform (Illumina) that was in use at the time of filing and even today, which generates DNA sequencing reads that are short and hence present particular challenges with respect to detection of certain kinds of mutations. While offering a specific improvement to DNA sequencing technology, the claimed inventions of the ’799 Patent are not pertinent to other techniques for genomic analysis that produces different types of data, such as the use of microarrays.

17. The claimed combination of steps in the '799 Patent is not routine and conventional, and neither are the individual steps claimed in the '799 Patent. By way of example only, the claims of the ’799 Patent recite the following steps:

> identifying a plurality of contig:reference descriptions of mutations by aligning the contig to said reference genome;
>
> identifying a plurality of read:contig descriptions by aligning each of the plurality of sequence reads to the contig; and
>
> combining the contig:reference descriptions with the read:contig descriptions to produce read:reference descriptions to map positional information of mutations found in the individual reads relative to the reference.

The individual step of generating "contig:reference descriptions of mutations," was not routine and conventional at the time, but rather represented a new approach to the assembly of DNA sequencing data. The same is true for the step of generating "read:contig descriptions," and the subsequent combination of the "contig:reference" and "read:contig" descriptions. Neither of these steps were in use prior to the claimed invention, and hence could not have been routine and conventional.

18. The claims of the '799 Patent encompass an inventive concept that improved upon the prior art. Specifically, by using the claimed technique, researchers can overcome the tradeoff in mutation detection capability that was inherent in the prior art and perform analyses that were previously thought intractable. This inventive concept is repeatedly detailed in the specification:

> By these methods, positional accuracy of reads is obtained and the limitations of a tradeoff between substitution sensitivity and deletion sensitivity are overcome. By combining data in this way, an accurate and sensitive interpretation of the nucleic acid is obtained and an accurate description of a genotype including an identity and a location of a mutation on an organism's genome is reported.

Id. at 2:53-58.

> The output of the local alignment, describing the read compared to the contig, can be combined with the output of the reference alignment, describing the contig compared to the reference. This combination gives, for any mutation detected in the nucleic acid, a description of that mutation relative to the reference genome. Wild type and mutant alleles including specific mutations can be identified. Mutation patterns previously thought to pose particular difficulty (e.g., long indels, indel-proximal substitutions, and indels near the ends of reads) are identified with fidelity. Methods of the invention can perform, with high-throughput data using existing computer power, sequencing and genotyping analyses that were previously computationally intractable.
>
> By combining information in this way, the limitations of a tradeoff between substitution sensitivity and deletion sensitivity is overcome. The output includes an accurate and sensitive interpretation of the subject nucleic. This provides an accurate description of a genotype including an identity and a location of a mutation on an organism's genome.

Id. at 4:38-57.

19. In or around August 2017, Natera began selling and offering to sell its commercial liquid biopsy test for cancer diagnostic, which it refers to by the trade name Signatera™. Ex. 2 at 17 [NTRA's 2017 10-K]. On information and belief, in or around May 2019, Natera began

selling or offering to sell the test for clinical use as a laboratory developed test at its CLIA laboratory operating in San Carlos, California ("CLIA laboratory"). Ex. 3 at 15 [NTRA's 2019 10-K].

20. Technical literature describing the technology underlying the Signatera™ test explains that it involves collecting tissue and whole blood samples from patients, performing analysis on them to determine somatic mutations, and generating a custom PCR panel for monitoring. *See* Ex. 4 [Signatera: A personalized, tumor-informed approach to detect molecular residual disease with high sensitivity and specificity].

21. When Natera performs the Signatera™ test, Natera infringes literally or under the doctrine of equivalents at least claim 1 of the '799 Patent. As set forth in the scientific literature, the Signatera™ test includes performing whole exome sequencing to compare the sequence from tumor tissue with that from matched whole blood to determine a set of 16 somatic single-nucleotide variants. *See* Exhibit 4 [A personalized, tumor-informed approach to detect molecular residual disease with high sensitivity and specificity]. On information and belief, Natera carries out identification of somatic mutations using the tool Genome Analysis Toolkit ("GATK") HaplotypeCaller or a method that implements a similar analysis, such as Mutect2. *See, e.g.*, Ex. 5 [https://gatk.broadinstitute.org/hc/en-us/articles/360037593851-Mutect2]. Upon information and belief, Natera carries out this process when it performs the Signatera™ test.

22. As an example, a preliminary and exemplary claim chart detailing Natera's infringement of at least claims 1 and 5 of the '799 Patent is attached hereto as Exhibit 6. This chart is not intended to limit Plaintiff's right to modify it, to provide other claim charts, or to allege that other activities of Natera infringe the identified claims, or any other claims of the '799 Patent or any other patents. Exhibit 6 is hereby incorporated by reference in its entirety. Each claim

element in Exhibit 6 that is mapped to the Signatera™ test shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each claim element is required.

COUNT I

23. Plaintiff repeats and re-alleges the foregoing paragraphs as if set forth specifically herein.

24. On March 31, 2020, the United States Patent and Trademark Office duly and legally issued U.S. Patent No. 10,604,799 B2, entitled "Sequence Assembly." A copy of the '799 Patent is attached as Exhibit 1.

25. Gregory Porreca and Caleb Kennedy are the sole and true inventors of the '799 Patent. By operation of law and as a result of written assignment agreements, Invitae obtained the entire right, title, and interest to and in the '799 Patent.

26. Natera has infringed and continues to infringe one or more claims of the '799 Patent pursuant to 35 U.S.C. § 271(a), literally or under the doctrine of equivalents, by performing within the United States without authority the Signatera™ test. As an example, attached as Exhibit 6 is a preliminary and exemplary claim chart detailing Natera's infringement of these claims of the '799 Patent. This chart is not intended to limit Plaintiff's right to modify the chart or to allege that other activities of Natera infringe the identified claims or any other claims of the '799 Patent or any other patents.

27. Exhibit 6 is hereby incorporated by reference in its entirety. Each claim element in Exhibit 6 that is mapped to Natera's Signatera™ test shall be considered an allegation within the meaning of the Federal Rules of Civil Procedure and therefore a response to each claim element is required.

DEMAND FOR JURY TRIAL

28. Pursuant to Federal Rule of Civil Procedure 38(b), Plaintiff demands a jury trial on all issues so triable.

PRAYER FOR RELIEF

WHEREFORE, Invitae prays for relief with respect to the '799 Patent as follows:

A. A judgement that Natera has infringed the '799 Patent and that the '799 Patent is valid;

B. Damages or other monetary relief, including, but not limited to, costs and pre- and post-judgement interest, to Plaintiff;

C. An order enjoining Natera and its officers, directors, agents, servants, affiliates, employees, divisions, branches, subsidiaries, parents, and all others acting in active concert therewith from further infringement of the '799 Patent; and

D. Such further and other relief as this Court deems proper and just, including, but not limited to, a determination that this is an exceptional case under 35 U.S.C. § 285 and an award of attorneys' fees and costs to Plaintiff in this action.

Dated: May 7, 2021

Respectfully submitted,

FARNAN LLP

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